REMARKS

Claims 1-18 are pending in the application. Claims 2-6, 8, 9, and 13-18, directed to non-elected inventions, are withdrawn from consideration. Applicant reserves the right to file the subject matter of the non-elected claims in one or more divisional applications.

Without acquiescing in the legal correctness of any outstanding objection or rejection, Applicant has amended the claims to expedite allowance of the instant application, as suggested by the Examiner.

Claims 1 and 10 are amended to clearly set forth the nature of the claimed invention. Claims 7 and 12 are cancelled, without prejudice or disclaimer. New claims 19-24 are added to further define the scope of the invention. Upon entry of the above amendments, claims 1, 7, 10-11, and 19-24 will be pending. To address the Examiner's concerns over original claim 12, new claim 24 is added to recite "wherein the nuclear matrix protein is not elevated in subjects afflicted with cystitis." Applicant respectfully requests the rejoinder of method claim 16 pursuant to the *Ochiai/Brouwer* guidelines. The foregoing amendments do not introduce new matter to the application, so entry thereof by the Examiner is respectfully requested.

Claim Objections

Applicant has cancelled claim 12 and revised claims 1 and 10 to recite the elected subject matter directed to anti-BLCA-6 antibody. Accordingly, the claim objections are moot.

Rejections Under 37 C.F.R. § 112, Second Paragraph

The Examiner alleges that claims 1 and 12 are indefinite for reciting the term "antigen." In addition, claim 12 is also allegedly indefinite for reciting the phrase "is not elevated in subjects."

In claim 1, Applicant has replaced the term "antigen" with the phrase "antigenic fragment." An antigenic fragment of BLCA-6 is clear and definite to those of ordinary skill in the art. It does not, however, encompass the specific embodiments provided in the Office Action. Moreover, the specification provides ample support for this scope of antigens, including representative working examples where peptide fragments of the BLCA proteins were used to generate antibodies that were shown to be capable of differentiating between normal and cancerous bladder cells.

Amendment of claim 1 and cancellation of claim 12 should overcome obviate the above-mentioned rejections.

In addition, the Examiner asserts that claims 1, 7, 10 and 11 are indefinite because the molecular weight of BLCA-6 protein is uncertain. The molecular weight of BLCA-6 protein as taught by Getzenberg *et al.* (1996) is different from what is being claimed in the present application.

In the accompanying Declaration (see attached unexecuted copy), Applicant explains the reasons for the existing discrepancy. Accordingly, the correct molecular weight for the BLCA-6 protein is 31-kD, as shown in Figure 1B of Appendix A (also see enclosed Appendix A). A more legible copy of Figure 1B is also enclosed, as Appendix B. Applicant will submit an executed copy of the Declaration in a Supplemental Response within two weeks of the submission of this Reply.

Applicant submits that claims 1, 7, 10 and 11 are inherently supported by the originally-filed specification.

In *Kennecott Corp. v. Kyocera International, Inc.*, 5 USPQ2d 1195 (Fed. Cir. 1987), the court addresses the issue of whether or not a limitation added to a product claim to state that the product had "a predominantly equiaxed microstructure" constituted "new matter." The specification nowhere referred to an "equiaxed microstructure" or suggested that the product in the examples had any equiaxed microstructure, predominant or otherwise.

However, the applicants showed that the product of the working examples in the original disclosure did possess this characteristic. In other words, they showed that the product of their invention produced as taught in the specification **necessarily and inherently** possessed "a predominantly equiaxed microstructure". The Court sided with the applicants, holding that:

> . . .anyone with a microscope would see the microstructure of the product of the [earlier] application. The disclosure in a subsequent patent application of an **inherent property** of a product does not deprive that product of the benefit of an earlier filing date. Nor does inclusion of a description of that property in later-filed claims change this reasonable result. [Emphasis supplied.]

In the instant case, the scope of claims 1, 7, 10 and 11 is supported and taught by the specification, and the claimed BLCA-6 protein necessarily and inherently possesses a molecular weight of 31-kD. The specification does teach one of the ordinary skill in the art to isolate the human BLCA-6 protein from human cells using the described techniques.

Therefore, even without reciting the correct molecular weight, one of ordinary skill in the art would inherently obtain a protein of about 31-kD.

In light of the foregoing amendments and remarks, Applicant respectfully requests the Examiner to reconsider and withdraw the rejections.

Rejections Under 37 C.F.R. § 112, First Paragraph

The Examiner alleges that claims 1, 7, 10, 11 and 12 do "not reasonably provide enablement for any antibody that specifically binds to any nuclear matrix protein or antigen thereof." To overcome this rejection, Applicant has amended the claims in accordance with the Examiner's suggestions.

Accordingly, withdrawal of the rejection under the first paragraph of section 112 is respectfully requested.

Rejection Under 37 C.F.R. § 101

According to the Examiner, claims 1, 7, 10 and 12 contain non-statutory subject matter. Applicant has amended these claims to recite that the claimed anti-BLCA-6 antibody is an "isolated or purified" antibody in accordance with the Examiner's suggestions. Accordingly, the rejection under section 101 has been obviated.

Rejection Under 37 C.F.R. § 102(b)

The Examiner rejected claim 12, as being unpatentable over Getzenberg *et al.* (*Cancer Res.* **56**: 1690-4, 1996). This rejection has been obviated due to the cancellation of claim 12

The Examiner further rejected claims 1, 7, 10, and 11-12 on the ground that the Briggman *et al.* (*Proc. Amer. Assn. Cancer Res.* **35**:15, Abstract No. 89 ,1994), as evidenced by Stedman's Medical Dictionary (1995), anticipates the subject matter of these claims. In particular, the Examiner alleges that Briggman's antibodies bind "to a NMP present in cancerous bladder cells..." that are directed to "the same antigen that the claimed antibodies bind." Based on this allegation, the Examiner concludes that Briggman has the same antibodies that are identical to the claimed antibody that binds to BLCA-6 protein. Applicant respectfully traverses the rejection.

During the prosecution of a related application (U. S. serial No. 09/143,369, filed August 28, 1998, now U. S. patent No. 6,280,956), the Examiner rejected the claimed antibodies directed to the BLCA proteins on similar grounds as in the present application. In

response, Applicant presented arguments that Briggman's antibody, as disclosed in his 1994 abstract, is distinct from the claimed antibodies and that Briggman's disclosure is not enabling. Accordingly, in replying to the present rejections, Applicant applies the same arguments that were previously presented.

At the outset, the evidence of record has established beyond any reasonable doubt that Briggman's antibody is the antibody that binds to NuMA and is distinct from the claimed BLCA-6 protein. Briggman and his colleagues described NuMA in Keese *et al., Critical Reviews in Eukaryotic Gene Expression*, 6(2 & 3):189-214 (1996) and in other later publications. NuMA is a 236 kDa protein (Keese, p. 138, left column) whereas the claimed antibody specifically binds to BLCA-6 protein having a much lower molecular weight (about 22 kDa). Moreover, unlike the claimed protein, NuMA is expressed in a number of non-bladder cells, including breast and prostate cancer cells (Keese, p. 203, left column). The difference in molecular weight alone is sufficient to eliminate any case of anticipation.

Even if the rejection maintains that Briggman's antibody was based on something other than NuMA (despite the overwhelming evidence to the contrary set forth below), then to that extent, Briggmann's reference is clearly non-enabling. Briggman, in his abstract, fails to provide proper guidance relating to the preparation of NuMA antibodies that were used to carry out the two-site immunometric assay as disclosed. One of ordinary skill in the art would not know how to produce any antibody based on Briggman alone. The Briggman abstract merely implies that Briggman possessed some antibody that could quantify an unspecified NMP in urine (which is almost certainly the NMP called "NuMA" as explained below). If that antibody is anything other than what is contained in the commercially available kit (which could have been purchased from Matritech and therefore could have been enabled) or another antibody, which binds NuMA, then it is not enabled by the prior art of record. Before a compound can be anticipated or obvious, there must be a known or obvious way of manufacturing the compound. That is, a reference must provide an enabling disclosure of how to obtain the compound. *In re Hoeksma*, 158 USPQ 596 (CCPA 1968). To the extent that Briggman's antibody is anything other than what is commercially available or which could have been produced based on the NuMA antigen, Briggman fails to even identify what that antigen might be, let alone, provide any disclosure as to how one of the ordinary skill in the art might begin to try to obtain it.

Nevertheless, it is quite clear that the Briggman reference is describing the NMP that is called "NuMA" in subsequent articles. The above-mentioned Keese article equates the antibodies 302.22 and 302.18 with the NMP22 test kit for detecting NuMA in urine and shows convincingly that these antibodies are not specific to bladder tissue. The Keese article cites an antibody that is similar to the antibody cited in the Briggman's abstract (1994).

In the Briggman abstract, the authors stated: "[a] two-site immunometric assay was developed to quantify a nuclear matrix protein (NMP) in voided urine." Keese, at page 203, cited an earlier work of Briggman (1992) on the use of a two site immunoassay to detect the presence of NuMA in the urine of bladder cancer patients. By definition, a two-site immunometric assays (also known as enzyme immunoassay) employs two forms of antibodies, with one being the probe antibody (antibody 302.22) and the second being the captured antibody (antibody 302.18). See Briggman's 1992 abstract, NCI Conference on Chemoprevention of Premalignant and Early Malignant Lesions of the Bladder, Taos, NM, 1992.

Moreover, Briggman's work in 1992, as cited by Keese (1996), clearly associates Briggman's earlier work directly with the NMP22 test kit. In fact, every journal article in 1992 that cites Briggman as an author or co-author links him directly with NMP22 and Matritech. Although the 1994 abstract of Briggman is directly connected only with Matritech, some of the authors' names in the 1994 abstract can also be found in the 1992 abstract (cited in Keese, 1996). It is, therefore, very unlikely that Briggman (and by inference, Matritech) has identified, developed, produced, and tested under clinical conditions, a completely different set of monoclonal antibodies that was never cited again in the literature as not being associated with NuMA or Matritech even after Briggman's initial work in 1992. By the same token, the disclosure of Briggman's work in 1994 was simply a continuation of his work done in 1992 (1992 abstract), which, in turn, served as an initial evaluation of NuMA antibodies for Matritech (as conducted by Briggman and his colleagues).

In light of the foregoing amendments and remarks, Applicant submits that neither Briggman alone (1994 abstract), nor in combination with the Stedman's Dictionary, is a patent-defeating reference. Accordingly, Applicant requests reconsideration and withdrawal of the novelty rejection.

Rejection Under 37 C.F.R. § 103

The Examiner rejected claim 12 as being unpatentable over Getzenberg *et al.* (Cancer Res. 56:1690, 1994), in view of Campbell (Monoclonal Antibody Technology, Elsevier Science Publishers, Chapter 1, p. 1-32, 1986).

To expedite the prosecution of the present application, Applicant has cancelled claim 12. Applicant respectfully requests that the rejection under section 103 be withdrawn.

CONCLUSION

In light of the following amendments and above-mentioned remarks, the Applicant believes that present application is now in condition for allowance. An early notice in this regard is earnestly solicited. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date 4/14/03

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Below are the marked up amended claim(s):

1. (Amended) An isolated or purified antibody that specifically binds to a nuclear matrix protein or an [antigen] antigenic fragment thereof, wherein said nuclear matrix protein is present in cancerous bladder cells but absent in normal bladder cells, and wherein the nuclear matrix protein is [selected from the group consisting of:

(a) BLCA-1 having a molecular weight of about 72 kD and a pI of about 7.70,

(b) BLCA-2 having a molecular weight of about 40 kD and a pI of about 7.50,

(c) BLCA-3 having a molecular weight of about 39 kD and a pI of about 6.27,

(d) BLCA-4 having a molecular weight of about 37 kD and a pI of about 6.24,

(e) BLCA-5 having a molecular weight of about 29 kD and a pI of about 5.80, and

(f)] BLCA-6 having a molecular weight of about **[22]** **31** kD and a pI of about 8.00.

10. (Amended) The antibody of claim [4] 1, wherein the [protein comprises the] antibody is directed against a peptide having an amino acid sequence of SEQ ID NO:4.